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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : G01N 27/02 — A1

(11) International Publication Number: WO 00/40955

(43) International Publication Date: 13 July 2000 (13.07.00)

(21) International Application Number: PCT/GB00/00001

(22) International Filing Date: 5 January 2000 (05.01.00)

(30) Priority Data:

9900103.4	5 January 1999 (05.01.99)	GB
9920217.8	27 August 1999 (27.08.99)	GB

(71) Applicant *(for all designated States except US)*: KAIKU LIMITED [GB/GB]; 27 Greenheys Businness Centre, Pencroft Way, Manchester M15 6JJ (GB).

(72) Inventors; and
Inventors/Applicants *(for US only)*: DOWDESWELL, Richard, Mark [GB/GB]; 1 Earlswood Mews, Hartford Road, Davenham, Cheshire CW9 8JA (GB). PAYNE, Peter, Alfred [GB/GB]; 16 The Stables, Tabley House, Knutsford, Cheshire WA16 0HA (GB). AMRANI, Mohammed, El Hassan [DZ/GB]; 33 Skerry Close, Brunswick, Manchester M13 9UD (GB).

(74) Agents: STUTTARD, Garry, Philip et al.; Urquhart–Dykes & Lord, Tower House, Merrion Way, Leeds LS2 8PA (GB).

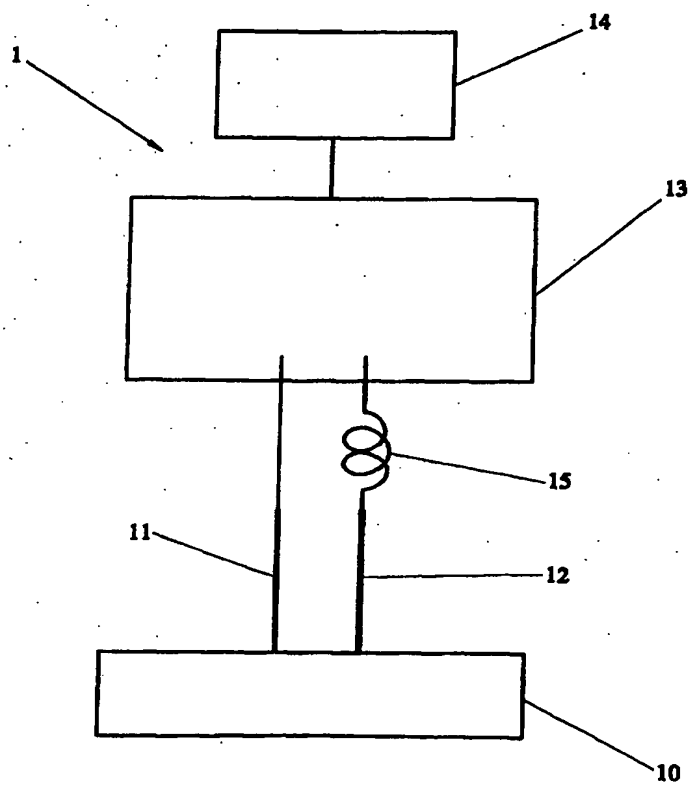
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: IMPEDANCE MEASUREMENTS OF BODILY MATTER

(57) Abstract

A method and apparatus for generating an impedance spectrum which is characteristic of a sample of bodily matter in a resonant circuit and which may be used to analyse the sample.



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Impedance Measurements of Bodily Matter

The present invention relates to a method and apparatus for generating an impedance spectrum which is characteristic of a sample of bodily matter in a resonant circuit.

Numerous conditions may give rise to abnormalities in bodily tissue (*eg* disease, wounding, infection or cancer). In many cases, diagnosis may only be possible by taking a biopsy for *ex vivo* analysis. As well as being invasive, this method is inefficient and unable to provide rapid online data. In addition, the removal of a biopsy may cause significant discomfort to the subject.

The electrical impedance spectrum exhibited by a sample of bodily matter is dependent upon its composition. Although bodily matter has previously been analysed by multi-frequency ac impedance measurements, the circuits used were not resonant. For example, it is known to use electrical impedance measurements to determine the status of a part of the body (see *inter alia* Dijkstra *et al*, Clinical Applications of Electrical Impedance Tomography, J Med. Eng. and Tech, 17, 3, 98-98).

The present invention is based on the recognition that the impedance spectrum of a sample of bodily matter which has been made part of a resonant electrical circuit is surprisingly sensitive to the characteristics of the sample of bodily matter and may be used to provide reliable and accurate detection of abnormalities in the sample (*eg* damaged or infected tissue). Moreover, the present invention is capable of providing information in real time whilst being substantially non-invasive.

Thus viewed from one aspect the present invention provides a method for generating an impedance spectrum which is characteristic of a sample of human or non-human bodily matter (*eg* tissue), said method comprising the steps of:

applying an electrical signal to the sample of bodily matter at each of a plurality of frequencies in a frequency range including a resonant frequency; and

measuring an impedance quantity at each of the plurality of frequencies in the frequency range whereby to generate the impedance spectrum.

Whilst not wishing to be bound by any theoretical consideration, it is nonetheless noted that an impedance quantity (Z^*) reflects the response of a sample of bodily matter (*eg* tissue) to an alternating electric field stimulus and may be considered as a type of transfer function expressing the ratio of the output voltage to input current. This transfer function is related to the composition of the sample of bodily matter being tested.

The impedance quantity may be considered equivalent to resistance (R) which is measured using direct current. However, in the frequency domain it is a complex number having both a real and an imaginary component expressed by:

$$Z^* = R+jX$$

(where X is the reactance which is a function of frequency and $j = \sqrt{-1}$). The resonant frequency is that frequency at which reactance is zero and may be regarded as the frequency at which the inductive and capacitive contributions to the reactance cancel out.

Impedance quantities which may be measured in accordance with the invention include the reactance (X) and

the phase angle (θ) which are by definition zero at the resonant frequency. A preferred impedance quantity is the dissipation factor (DF) defined as:

$$DF = R/X$$

DF is a measure of the energy dissipated in a circuit by the resistive heating relative to the energy stored in a circuit by capacitive and inductive mechanisms. DF reaches a maximum as X reaches zero (*ie* as the resonant frequency is reached).

In one embodiment of the invention, the electrical signal is a time varying electrical signal. Preferably, the time varying electrical signal is an alternating current (ac) signal.

The measurement of the impedance quantity may comprise a time to frequency domain transformation of the time varying electrical signal. The steps involved in such a measurement will be generally familiar to those skilled in the art (see for example Perturbation Signals for System Identification, *ed* K Godfrey, Prentice Hill, 1993, UK). The time varying electrical signal may be periodic and may comprise any suitable function or code *eg* a pseudo random binary sequence (PRBS), a Golay code, a Walsh function, a Huffman sequence or any other suitable coded sequence. Other suitable signals, codes or methodologies such as white Gaussian noise or wavelet analysis may be employed and will be generally familiar to those skilled in the art (see for example Signal Processing Methods for Audio Images and Telecommunications, *ed* P M Clarkson and H Stork, Academic Press, London, 1995).

The electrical signal may be applied by at least two electrodes. The electrodes may be in direct or indirect electrical contact with the sample of bodily matter. For

example, an insulating layer may be placed over one or more of the electrodes so that the electrodes are in indirect electrical contact with the sample of bodily matter.

In a preferred embodiment of the method of the invention, the electrical signal may be applied by one or more microelectrodes of the type generally or specifically disclosed in WO-A-99/60392 (Farfield Sensors Limited) or specifically claimed therein.

Alternatively, the electrical signal may be applied via at least two windings. The windings may be in direct or indirect electrical contact with the sample of bodily matter.

A means for varying the frequency of the applied electrical signal may be used to apply the electrical signal at a plurality of frequencies in a range including the resonant frequency. For example, at least one inductor or one or more quartz crystal resonators may be used. Conveniently, the means for varying the frequency of the applied electrical signal ensures that the resonant frequency is below about 1MHz. At such a resonant frequency, problems associated with instrumentation and digitisation are generally reduced.

In a preferred embodiment, the method of the invention comprises the step of comparing the impedance spectrum of an abnormal sample of bodily matter with the impedance spectrum of a normal (*ie* healthy) sample of bodily matter to deduce the relative characteristics of the normal and the abnormal sample. The term "abnormal sample of bodily matter" may include *inter alia* cancerous, scarred, infected or diseased tissue.

For example, the impedance spectra may be compared to deduce a shift in the resonant frequency or a difference in

the magnitude of the impedance quantity at or near to the resonant frequency. In turn, the relative characteristics of the abnormal and normal sample of tissue may be deduced in a further step.

The method of the invention may be used to detect abnormalities in normal bodily tissue. For example, the method may be advantageously used to detect abnormalities in external bodily tissue including *inter alia* skin abnormalities, tooth decay, gum disease or cancerous growths. However the method may equally be used on interior bodily tissue to detect abnormalities such as bone abnormalities or cancerous tissue.

In a preferred embodiment, the method of the invention comprises the following steps:

applying a first electrical signal to a first sample of bodily matter at each of a plurality of frequencies in a first frequency range including a resonant frequency;

measuring an impedance quantity at each of the plurality of frequencies in the first frequency range whereby to generate an impedance spectrum of the first sample;

applying a second electrical signal to a second sample of bodily matter at each of a plurality of frequencies in a second frequency range including a resonant frequency;

measuring an impedance quantity at each of the plurality of frequencies in the second frequency range whereby to generate an impedance spectrum of the second sample;

comparing the impedance spectrum of the first sample and the impedance spectrum of the second sample; and

deducing the relative characteristics of the first and the second sample of bodily matter.

By way of example, the first sample may be a normal sample of bodily matter (*eg* healthy tissue) and the second sample may be an abnormal sample of bodily matter. The step of comparing may comprise calculating the shift in resonant frequency between the normal sample of bodily matter and the abnormal sample of bodily matter.

The sensitivity of the method of the invention is such that the shift in the resonant frequency between a sample of normal and a sample of abnormal bodily matter may be significant and may be a downward or an upward shift. For example, a downward shift in resonant frequency is typically characteristic of a sample of diseased skin *vis a vis* a sample of normal skin whilst an upward shift in resonant frequency is typically characteristic of a sample of scar tissue *vis a vis* a sample of normal skin. Typically the shifts are as significant as -90kHz and +100kHz respectively.

Alternatively, the step of comparing may comprise calculating a change in the magnitude of the impedance quantity at the resonant frequency. This is useful where the impedance quantity is the dissipation factor.

Viewed from a further aspect the present invention provides an apparatus for generating an impedance spectrum which is characteristic of a sample of human or non-human bodily matter (*eg* tissue), said apparatus comprising:

electrical signal applying means adapted to apply a time varying electrical signal to the sample of bodily matter at each of a plurality of frequencies in a frequency range including a resonant frequency; and

measuring means for measuring an impedance quantity characteristic of the sample of bodily matter at each of the plurality of frequencies in the frequency range whereby to generate the impedance spectrum.

In an embodiment of the apparatus of the invention, the electrical signal applying means is capable of applying an ac signal of variable frequency.

In an embodiment of the apparatus of the invention, the electrical signal applying means is capable of applying a time varying electrical signal which is periodic.

The electrical signal applying means may be adapted for use *ex vivo* or *in vivo* (externally or internally) as required. The electrical signal applying means may be capable of being positioned in direct or indirect electrical contact with the bodily matter.

The electrical signal applying means may comprise a means for varying the frequency of the electrical signal to apply the electrical signal at a plurality of frequencies in a range including the resonant frequency. For example, the apparatus may further comprise at least one inductor or at least one quartz crystal resonator. Conveniently, the means for varying the frequency of the electrical signal is arranged so that the resonant frequency is below about 1MHz. At such a resonant frequency, problems associated with instrumentation and digitisation are generally reduced.

The electrical signal applying means may comprise at least two electrodes. The electrodes may be capable of being positioned in direct or indirect electrical contact with the bodily matter. For example, one or more of the electrodes may comprise an outer insulating layer so that the electrodes are capable of being positioned in indirect electrical contact with the sample of bodily matter.

Numerous electrode materials, sizes and configurations are suitable (as desired) for the preferred embodiment.

Generally, the configuration and material may be tailored to the end use. For example, planar electrodes may be used where the sample of bodily matter comprises the skin. Such planar electrodes may be rectangular or half ring configurations as desired. Multiple electrode arrangements may be used where desired. Modulation of the applied electrical field strength is possible to find the optimum working field strength or to provide additional information on the tissue sample.

In a preferred embodiment of the apparatus of the invention, the electrical signal applying means comprises one or more microelectrodes of the type generally or specifically disclosed in WO-A-99/60392 (Farfield Sensors Limited) or specifically claimed therein.

The electrical signal applying means may comprise at least two windings. The windings may be capable of being positioned in direct or indirect electrical contact with the bodily matter. For example, the windings may be potted in a casing of an inert material. This embodiment acts in a similar manner to a transformer *ie* wherein one winding is energised as a primary winding and drives a second winding which acts as a secondary winding. A current may be induced in the secondary winding with an efficiency which depends on the impedance of the medium between the primary and secondary windings.

In an embodiment of the invention, the electrical signal applying means comprises a probe adapted to be inserted into a bodily cavity and to enable measurement of the impedance spectrum characteristic of the surrounding tissue. The probe may be useful in internal use *eg* in the detection of cancer (*eg* cervical cancer). The probe may

comprise one or more suitably shaped electrodes (*eg* needle electrodes) insertable into the bodily cavity.

In an embodiment of the apparatus of the invention, the measuring means may comprise an impedance analyser.

In an embodiment of the apparatus of the invention, the measuring means may be capable of performing a time to frequency domain transformation of the time varying electrical signal.

Viewed from a yet further aspect the present invention provides the use of an apparatus as hereinbefore defined for generating an impedance spectrum at each of a plurality of frequencies in a frequency range including a resonant frequency which is characteristic of a sample of human or non-human bodily matter. Preferably the sample is an exterior part of the human or non-human body (*eg* the skin).

Viewed from a yet still further aspect the present invention provides a kit of parts suitable for generating an impedance spectrum at each of a plurality of frequencies in a frequency range including a resonant frequency which is characteristic of a sample of human or non-human bodily matter, said kit comprising:
at least two electrodes for applying alternating current to the sample of bodily matter;
an inductor; and
an impedance analyser capable of measuring an impedance quantity at each of the plurality of frequencies in the frequency range including the resonant frequency whereby to generate the impedance spectrum.

Methods and apparatus in accordance with the invention will now be described in a non-limitative sense with reference to the accompanying Figures in which:

Figure 1 is a schematic illustration of a first embodiment of an apparatus of the invention;

Figure 2 illustrates dissipation factor as a function of frequency for samples of undamaged skin and scar tissue; and

Figure 3 illustrates dissipation factor as a function of frequency for samples of non-infected and infected skin.

In a first embodiment of the apparatus of the invention shown schematically in Figure 1 and designated generally by reference numeral 1, a time varying electrical signal was applied to a sample of bodily matter 10 by two nickel coated steel electrodes 11 and 12 in direct contact therewith. In the first example, the sample of bodily matter was tissue on the back of a human subject's hand which exhibited a small dry scar whose surrounding area was slightly reddened. An inductor 15 was provided in series with electrodes 11 and 12 to ensure that the circuit was capable of resonating. The value of the inductor 15 used (324mH) was such that the resonant frequency occurred within a tractable range *ie* at around 1 MHz or less. The applied voltage was 0.2 volts peak to peak which caused minimal discomfort to the subject.

An ac signal of variable frequency was applied and the dissipation factor was measured as a function of the frequency of the applied signal over a frequency range which includes a resonant frequency. The dissipation factor was measured by an impedance analyser 13 (Hewlett Packard 4192A). Data were transferred to a personal computer 14 for further analysis.

The electrodes 11 and 12 were placed approximately 5mm from the scar tissue and the dissipation factor spectrum characteristic of the normal sample of tissue was measured at 10 kHz intervals in the range 1 to 800 kHz. This measurement was repeated and the results are shown in Figure 2 (reference 21). The electrodes 11 and 12 were then placed onto the scar and a similar reading (reference 22) was obtained for the abnormal (scar) tissue also shown in Figure 2.

It will be seen that the scar tissue and the normal tissue exhibit a significantly different impedance spectrum. The resonant frequency observed for scar tissue is about 100 kHz higher than the resonant frequency of normal tissue. It will also be noted that the upward shift in resonant frequency is accompanied by an apparent increase in the value of the dissipation factor. The maximum calculated value of the dissipation factor is critically dependent upon the value of the reactance as it approaches zero. The calculated value of the maximum dissipation factor is therefore dependent upon the frequency step size and its proximity to the true resonant frequency. The latter is likely to be temperature dependent although given time for any subject to acclimatise to the environment in which the measurements are conducted this may be controlled. Notwithstanding these comments, it is believed that the magnitude of the dissipation factor will provide useful information additional to that provided by the resonant frequency.

Figure 3 illustrates the dissipation factor as a function of frequency for a normal and an abnormal sample of skin tissue from the palm of a subject who has an area of diseased skin (dermatitis). Impedance measurements over the range 1-870 kHz were conducted. The normal sample exhibited a resonant frequency at about 460kHz while the abnormal (diseased) sample was considerably lower at about 370kHz

(references 31 and 32 respectively). It will be noted that the downward shift in resonant frequency characteristic of diseased skin is opposite to the upward shift in resonant frequency characteristic of scar tissue. This leads to the possibility of distinguishing two skin conditions.

CLAIMS

1. A method for generating an impedance spectrum which is characteristic of a sample of human or non-human bodily matter, said method comprising the steps of:

applying an electrical signal to the sample of bodily matter at each of a plurality of frequencies in a frequency range including a resonant frequency; and

measuring an impedance quantity at each of the plurality of frequencies in the frequency range whereby to generate the impedance spectrum.

2. A method as claimed in claim 1 wherein said bodily matter is bodily tissue.

3. A method as claimed in claim 1 or 2 wherein said impedance quantity is the dissipation factor.

4. A method as claimed in any preceding claim wherein said electrical signal is a time varying electrical signal.

5. A method as claimed in claim 4 wherein the time varying electrical signal is periodic.

6. A method as claimed in claim 4 or 5 wherein said time varying electrical signal is an alternating current signal.

7. A method as claimed in any of claims 4, 5 or 6 wherein the measurement of the impedance quantity is a time to frequency domain transformation of the time varying electrical signal.

7. A method as claimed in any preceding claim comprising the step of comparing the impedance spectrum of an abnormal sample of bodily matter with the impedance spectrum of a

normal sample of bodily matter to deduce the relative characteristics of the normal and abnormal sample.

8. A method as claimed in claim 7 wherein the impedance spectra may be compared to deduce a shift in the resonant frequency or a difference in the magnitude of the impedance quantity at or near to the resonant frequency.

9. A method as claimed in any preceding claim comprising the steps of:

applying a first electrical signal to a first sample of bodily matter at each of a plurality of frequencies in a first frequency range including a resonant frequency;

measuring an impedance quantity at each of the plurality of frequencies in the first frequency range whereby to generate an impedance spectrum of the first sample;

applying a second electrical signal to a second sample of bodily matter at each of a plurality of frequencies in a second frequency range including a resonant frequency;

measuring an impedance quantity at each of the plurality of frequencies in the second frequency range whereby to generate an impedance spectrum of the second sample;

comparing the impedance spectrum of the first sample and the impedance spectrum of the second sample; and

deducing the relative characteristics of the first and the second sample of bodily matter.

10. A method as claimed in claim 9 wherein the first sample is a normal sample of bodily matter and the second sample is an abnormal sample of bodily matter.

11. A method as claimed in claim 9 or 10 wherein the comparing step comprises: calculating the shift in resonant

frequency between the normal sample of bodily matter and the abnormal sample of bodily matter.

12. A method as claimed in claim 11 wherein the shift in resonant frequency is a downward shift in resonant frequency.

13. A method as claimed in claim 11 wherein the shift in resonant frequency is an upward shift in resonant frequency.

14. A method as claimed in claim 11 wherein the shift in resonant frequency is in the range -90kHz to +100kHz.

15. A method as claimed in claim 9 or 10 wherein the comparing step comprises: calculating a change in the magnitude of the impedance quantity at or near to the resonant frequency.

16. A method as claimed in any preceding claim conducted *in vivo* wherein the sample of bodily matter is exterior or interior body tissue.

17. A method as claimed in any preceding claim wherein the sample of bodily matter is selected from the group consisting of cancerous, scarred, infected or diseased tissue.

18. An apparatus for generating an impedance spectrum which is characteristic of a sample of human or non-human bodily matter, said apparatus comprising:

electrical signal applying means adapted to apply a time varying electrical signal to the sample of bodily matter at each of a plurality of frequencies in a frequency range including a resonant frequency; and

measuring means for measuring an impedance quantity characteristic of the sample of bodily matter at each of the

plurality of frequencies in the frequency range whereby to generate the impedance spectrum.

19. An apparatus as claimed in claim 18 wherein the electrical signal applying means is capable of applying a time varying electrical signal which is periodic.

20. An apparatus as claimed in 18 or 19 wherein the electrical signal applying means is adapted for use *ex vivo* or *in vivo* (externally or internally)

21. An apparatus as claimed in any of claims 18 to 20 wherein the electrical signal applying means is capable of being positioned in direct or indirect electrical contact with the bodily matter.

22. An apparatus as claimed in any of claims 18 to 21 wherein the electrical signal applying means comprises a means for varying the frequency of the electrical signal to apply the electrical signal at a plurality of frequencies in a range including the resonant frequency.

23. An apparatus as claimed in claim 22 wherein the means for varying the frequency of the electrical signal comprises at least one inductor or at least one quartz crystal resonator.

24. An apparatus as claimed in either of claims 22 or 23 wherein the means for varying the frequency of the electrical signal is arranged so that the resonant frequency is below about 1MHz.

25. An apparatus as claimed in any preceding claim wherein the electrical signal applying means comprises at least two

electrodes capable of being positioned in direct or indirect electrical contact with the bodily matter.

26. An apparatus as claimed in any of claims 18 to 24 wherein the electrical signal applying means comprises at least two windings capable of being positioned in direct or indirect electrical contact with the bodily matter.

27. An apparatus as claimed in any of claims 18 to 26 wherein the electrical signal applying means comprises a probe adapted to be inserted into a bodily cavity and to enable measurement of the impedance spectrum characteristic of the surrounding tissue.

28. An apparatus as claimed in any of claims 18 to 27 wherein the measuring means comprises an impedance analyser.

29. An apparatus as claimed in any of claims 18 to 27 wherein the measuring means is capable of performing a time to frequency domain transformation of the time varying electrical signal.

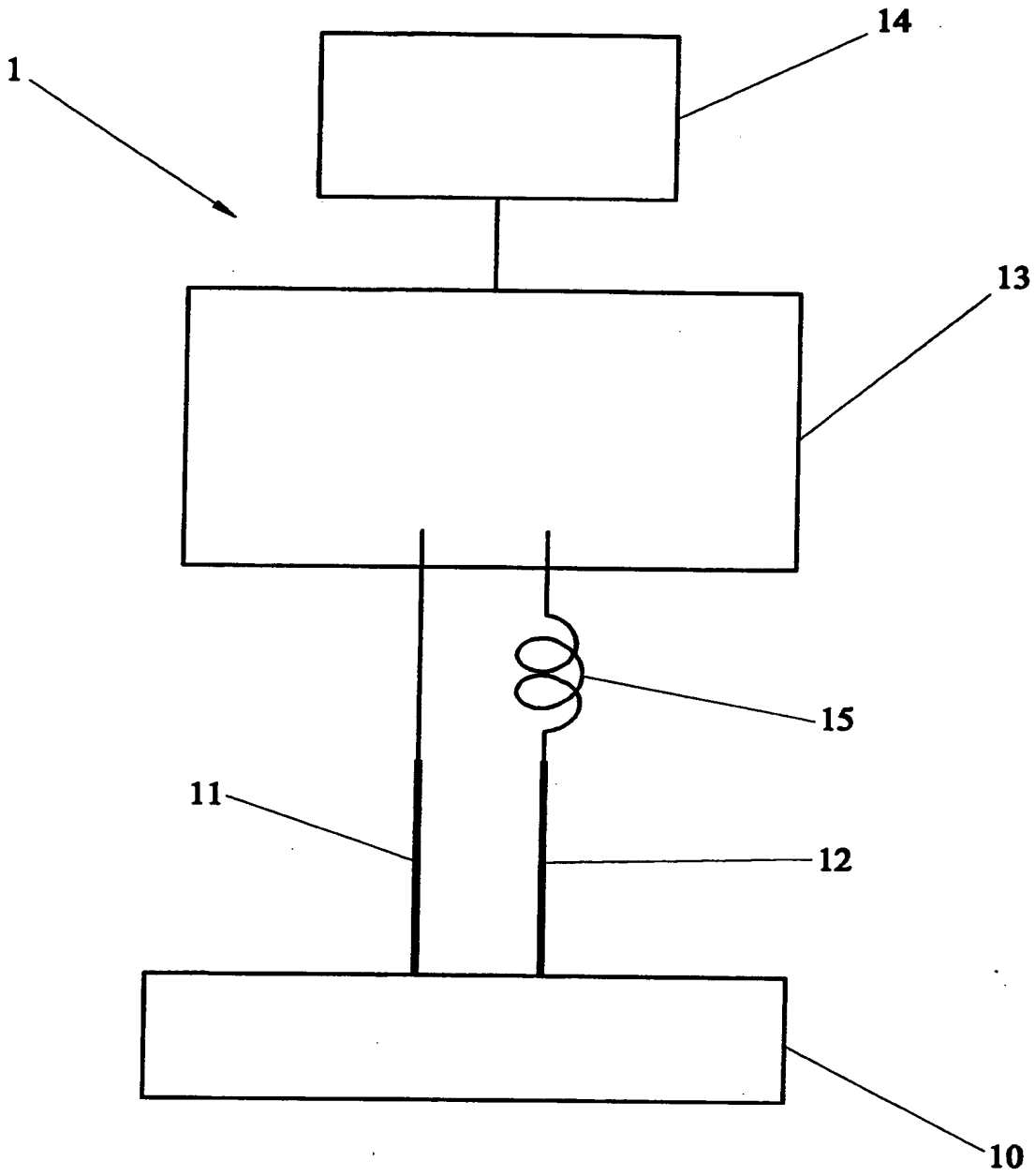
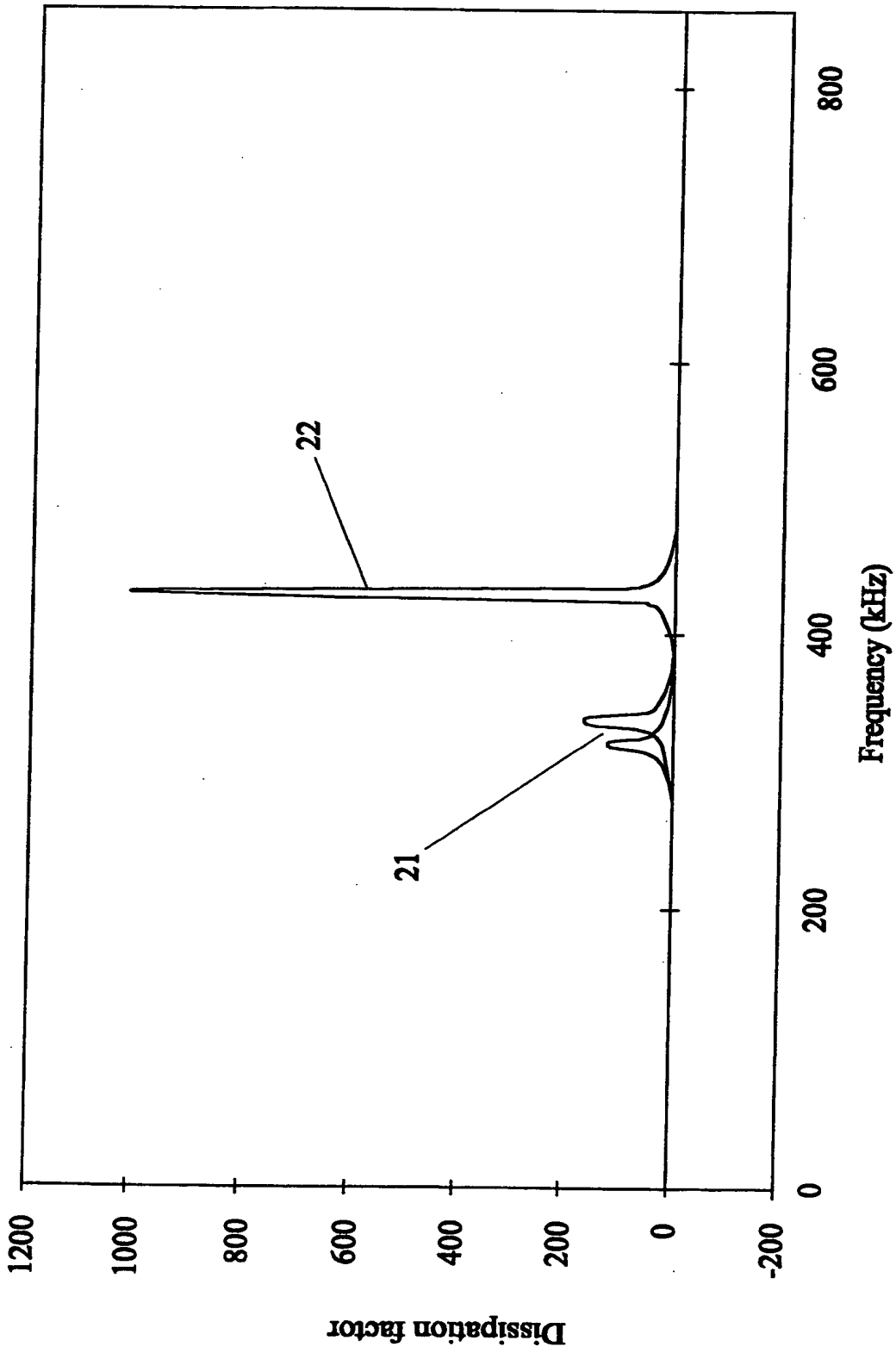


FIG. 1


22
21
Frequency (kHz)
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200
400
600
800
Dissipation factor
-200
0
200
400
600
800
1000
1200

FIG. 2

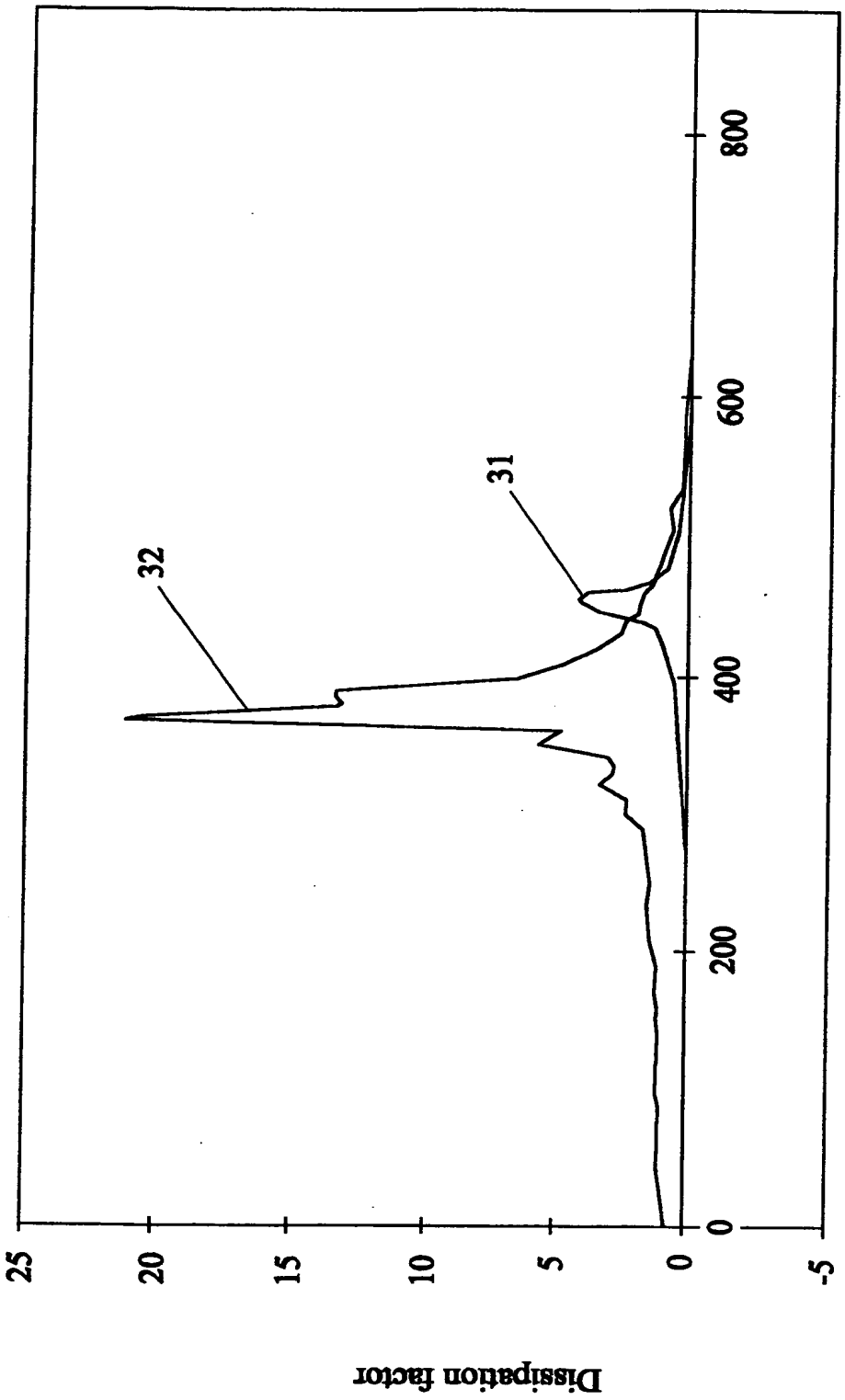
Dissipation factor
25
20
15
10
5
0
-5
0
200
400
600
800
Frequency (kHz)
31
32

FIG. 3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/00001

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N27/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N A61B G01R

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 34808 A (PHARMACIA BIOTECH AB ;LING TORBJOERN (SE); MONTELIUS LARS (SE); TE) 21 December 1995 (1995-12-21) page 1, line 3 - line 5 page 4, line 14 - line 27	1,4,5, 18,19,22
Y	US 5 746 214 A (BARBER DAVID CHARLES ET AL) 5 May 1998 (1998-05-05) claims 1,6,8,9,14	1,2,16, 21,26
A	column 1, line 55 - line 67	3-15, 17-20, 22-25, 27-29

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 April 2000	17/04/2000

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

.rnational Application No
PCT/GB 00/00001

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document. with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 819 648 A (KO HARVEY W) 11 April 1989 (1989-04-11) column 1, line 19 - line 28 column 3, line 40 - line 60 column 5, line 34 - line 55 column 6, line 3 - line 30	1,2,16, 21,26
A	column 2, line 24 - line 27	3-15, 17-20, 22-25, 27-29
A	EP 0 865 763 A (NTE S A) 23 September 1998 (1998-09-23) claim 1 column 1, line 28 - line 34	1-29
A	RIGAUD B ET AL: "TISSUE CHARACTERIZATION AND MODELING BY ELECTRICAL BIOIMPEDANCE SPECTROMETRY" PROCEEDINGS OF THE ANNUAL INTERNATIONAL CONFERENCE OF THE IEEE ENGINEERING IN MEDICINE AND BIOLOGY SOCIETY,US,NEW YORK, IEEE, vol. 16, 1994, pages 866-867, XP000552373 ISBN: 0-7803-2051-4 the whole document	1-29
A	THOMAS B J ET AL: "Bioimpedance Spectrometry in the Determination of Body Water Compartments: Accuracy and Clinical Significance" APPLIED RADIATION AND ISOTOPES,GB,PERGAMON PRESS LTD., EXETER, vol. 49, no. 5-6, 6 May 1998 (1998-05-06), pages 447-455, XP004110545 ISSN: 0969-8043 page 450 -page 452 figure 1	1-29

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/00001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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